New Mexico Cancer Care Alliance
University of New Mexico Cancer Center

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PROTOCOL
PROTOCOL NUMBER: INST 1211

A Pilot Randomized, Placebo Controlled, Double Blind Study of Omega-3 Fatty Acids to Prevent Paclitaxel Associated Acute Pain Syndrome

Principal Investigators:

Zoneddy Dayao, MD
University of New Mexico Cancer Center
1201 Camino de Salud NE, MSC07 4025
Albuquerque, NM 87131-001
(505) 272-5490
FAX: (505) 272-7799
zdayao@salud.unm.edu

Debra Barton, RN, PhD, AOCN, FAAN
Mayo Clinic
200 First Street S.W.
Rochester, MN 55905
(507) 255-3812
FAX (507) 538-8300
barton.debra@mayo.edu

Co-Investigator(s):

Melanie Royce, MD
University of New Mexico Cancer Center
1201 Camino de Salud NE, MSC07 4025
Albuquerque, NM 87131-001
(505) 925-0405
FAX: (505) 272-7799
mroyce@salud.unm.edu

Study Sites: New Mexico Cancer Care Alliance: University of New Mexico, Lovelace Health Systems, Presbyterian Healthcare Services, Memorial Medical Center, Christus St. Vincent Regional Medical Center, Hematology-Oncology Associates, New Mexico Cancer Care Associates

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and all attachments as necessary. It provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Zoneddy Dayao, M.D.

PI Signature: _____

Date: _____

Background and Rationale (including feasibility)

Paclitaxel, a widely used chemotherapeutic agent, is associated with several well-known side effects including neuropathy and generalized body aches (1). The latter has recently been described as paclitaxel- associated acute pain syndrome (P-APS) and often occurs in the 1st 3-4 days after administration (2). It affects about 58-90% of patients (2, 10). Previously, these symptoms have been described as myalgias and arthralgias (1). However, recent data support that P-APS may in fact be an early manifestation of neuropathy, as opposed to being musculoskeletal in origin. For instance, it was noted that patients with higher P-APS pain scores with the first dose of paclitaxel are at risk for developing chronic neuropathy (2, 3).

P-APS can be severe, and may require use of potent analgesics for symptom control. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as frontline therapy. However, there is concern over side effects including gastrointestinal bleeding and acute renal injury. Many therapies have been studied including steroids (4), glutamine (5), antihistamine (6), opioid analgesics, and herbs (7), with variable results.

Low dose oral prednisone starting 24 hours after completion of chemotherapy and continued for a total of 5 days has been previously reported to result in substantial improvement in symptomatology (3). However, this study was limited due to the small sample size. In addition, given the variable schedule of paclitaxel ranging from weekly to every 3 weeks, this regimen could result in a significant amount of prednisone and can increase the risk of side effects over time.

In a placebo-controlled, double blind randomized crossover trial, the effect of glutamine on paclitaxel associated myalgias and arthralgias showed that glutamine, although well tolerated, had no effect on the development and severity of symptoms, as reported by the treating physician and by patient log (5).

Oral low-dose antihistamine, in the form of terfenadine 60 mg at the onset of pain and subsequently, has been reported to be temporarily effective in controlling paclitaxel-induced myalgia and /or dysesthesia (5). However, this study was also limited by its sample size with only 9 patients included.

Currently, there is no standard of care for P-APS. Since paclitaxel is a commonly used chemotherapeutic agent and P-APS is common and can be debilitating to some patients, an agent with a favorable toxicity profile that may prevent P-APS and possibly prevent the development of neuropathy will have significant clinical utility.

Data on the Pathophysiology of Paclitaxel-Associated Acute Pain Syndrome

The mechanism of P-APS is currently unknown. For many years, these subacute aches and pains were described as myalgias/ arthralgias based on patient reported symptoms. The self-limited course led to a hypothesis that symptoms are possibly the result of an inflammatory reaction to paclitaxel (1,3). More recently, Loprinzi et al reported the natural history of P-APS (2,3). In this study, P-APS symptoms were assessed in 94 patients using patients' daily symptom log with 10 items assessing pain symptoms and used of pain medication, adapted from Cleeland's Brief Pain Inventory (Appendix I). In addition, a 22-item summary questionnaire regarding symptom characteristics was given after paclitaxel use. Chemotherapy-induced peripheral neuropathy (CIPN) symptoms were assessed using the validated EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire (QLQ)-CIPN-20 given at baseline and weekly after each paclitaxel dose.

With regards to the P-APS, it was noted that the most common manifestation was a diffuse achiness mainly involving the legs, hips and lower back, typically evolving over 1-4 days. Interestingly, in the weekly paclitaxel treatment group, the initial pain experienced with the first treatment did not predict the severity of pain with additional doses, but appeared to predict the severity of symptoms associated with . peripheral neuropathy, predominantly sensory, which evolved over the 12-week period of treatment. This is the first study showing that the P-APS may in fact be an early manifestation of neuropathy and is associated with the development of chronic neuropathy (2, 3).

One mechanism proposed for P-APS is an early inflammatory process characterized by macrophage activation in both the DRG and peripheral nerve occurring shortly after paclitaxel therapy (9). Morphologic alterations in DRG satellite cells have been noted and upregulation of proinflammatory cytokines have been hypothesized as early events in the development of neuropathy (9). Therefore, it is possible that paclitaxel-induced neuropathic pain may be mediated by proinflammatory cytokines. If P-APS and chronic neuropathy are indeed part of a continuum, the inflammatory pathway would be a reasonable target for therapy.

The exact mechanism on how paclitaxel eventually leads to the development of neuropathy is still not understood. Taxanes promote stabilization of microtubules leading to disruption of normal cell division, and eventually resulting in cell death. Results of a study showed that short-term administration of paclitaxel induces mainly reversible changes in the peripheral nerves and spinal roots (8). Microtubules seem to be the main target of paclitaxel neurotoxicity, in much the same way as has been described for its antineoplastic activity. It has been hypothesized that microtubule-dependent axonal transport is disrupted by paclitaxel. Abnormal aggregation of microtubules in neuronal cells is hypothesized to contribute to neurosensory abnormalities leading to impairment of axonal transport (8).

Taken together, an intervention with both anti-inflammatory as well as neuroprotective properties would be an ideal candidate for testing in the prevention of P-APS and subsequent development of peripheral neuropathy.

Rationale for Studying Omega 3 Fatty Acids to Prevent or Ameliorate P-APS

Omega 3 Fatty Acids: Anti-Inflammatory Properties and P-APS.

Essential polyunsaturated fatty acids (PUFA) have two major families, the omega-6 (n-6) and omega-3 (n-3). The 20 carbon (n-3) and (n-6) fatty acids compete for the same enzymes and therefore, the intake of one omega fatty acid will diminish the metabolism of the other (10,15).

Arachidonic Acid (AA) is a primarily diet-derived 20 carbon omega-6 PUFA which serves as a precursor of proinflammatory metabolites such as prostaglandins, thromboxanes and leukotrienes (10). These eicosanoids are involved in modulating the intensity and duration of an inflammatory response. Cyclooxygenase (COX) enzymes are the rate limiting enzymes in the conversion of AA to prostaglandin E2 (PGE2) and are a target for therapy, of which the most widely studied are the NSAIDS.

Long chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are common dietary supplements. They have well established anti-inflammatory properties which serve as the basis for their use in therapeutic trials in inflammatory conditions (10, 11).

EPA competes with AA for enzymatic metabolism, thereby decreasing inflammatory derivatives.

Recently, omega-3 PUFAs have also been identified as precursors of anti-inflammatory mediators called protectins and resolvins. Resolvins occur in the resolution phase of inflammation. Protectin D1 was

initially found to decrease damage of brain ischemia-reperfusion injury and thus named neuroprotectin D1 (12-14).

Several clinical studies have reported the pain relieving effects of omega 3 fatty acids for inflammatory joint diseases. In a recent meta-analysis of 17 trials, supplementation of omega-3 fatty acids for 3-4 months resulted in reduction in patient reported pain severity, duration of morning stiffness and amount of NSAID consumption (11).

As noted above, there is evidence that early inflammatory processes are observed in paclitaxel induced nerve damage. This may in part account for the symptoms of P-APS, and sustained inflammation may lead to downstream effects responsible for evolution of peripheral neuropathy (8, 9). Omega-3 fatty acids consumption can attenuate the production of pro-inflammatory metabolites. In addition, it can generate local mediators that facilitate resolution of inflammation (12-14). Thus, if P-APS is indeed mediated by inflammation, the anti-inflammatory activity of omega-3 fatty acids may be one mechanism to prevent P-APS. Additionally, given its well established safety profile, it may be an attractive alternative to NSAIDS.

Omega 3 Fatty Acids: A Dietary Supplement with Neuroprotective Properties

The nervous system is richly endowed with omega-3 fatty acids, primarily DHA. Omega-3 fatty acids may act as natural neuroprotective agents, as well as key components in nerve hemostasis. Several studies have reported the role of omega-3 fatty acids in maintaining nerve integrity and function (16, 21). Long chain n-3 PUFAs such as docosahexaenoic acid (DHA) have been shown to have promising in the treatment of a broad range of neurodegenerative conditions (16).

Several preclinical models have shown the neuroprotective effect of DHA in models of spinal cord injury (17- 19). A mouse model has recently been used comparing groups with different fatty acid profiles (19). One group expressed the *fat-1 gene* from Caenorhabditis elegans, which encodes a fatty acid desaturase, the enzyme that converts n-6 into n-3 PUFAs, leading to enrichment in tissue n-3 PUFA levels (low n-6/n-3 ratio). This was compared to the group that had a high n-6/ n-3 ratio as well as to wild type strain. Utilizing in vitro and in vivo injury models, neurite growth, axonal regeneration, sensory and motor function were assessed and compared. Interestingly, the dorsal root ganglion neurons from fat-1 mice (n-3 enriched) had significant increase in neurite outgrowth and improved neuronal survival after injury. The omega-3 enriched group did not exhibit an increase in neuronal cell death after mechanical or hypoxic injury, in contrast to the 2 groups where hypoxia resulted in neuronal cell death in the order of 2.3 - 2.6 fold increase. The mice expressing the fat-1 gene showed a more complex neurite outgrowth phenotype, with neurons displaying both longer neurites and branches, supporting the notion that n-3 PUFA level had improved neuroregenerative potential. Interestingly, the in vivo experiments also showed that the higher tissue n-3 PUFA group also exhibited a faster recovery of sensory loss, as assessed by mechanical stimulation thresholds. Even after a severe form of injury such as a crush injury, recovery of sensation was faster in the group that was enriched for omega-3.

In the clinical setting, omega-3 fatty acids have been studied in a wide spectrum of neurodegenerative disorders (21- 24). Alzheimer's disease, a progressive neurodegenerative disease, has been reported to strongly correlate with decreases in omega -3 fatty acid levels in the brain and peripheral tissue compared to age-related controls (22). Epidemiological studies have also shown a correlation between lower levels of dietary omega-3 fatty acids and the development of Alzheimer's disease (23), suggesting a

neuroprotective effect. Similar observations have been seen in Parkinson's disease, a neurodegenerative disorder of the basal ganglia (24). Dietary interventions however have shown conflicting results.

There are also emerging data on the role of omega-3 fatty acid supplementation in acute neurologic injuries. As an example, it was reported that administration of moderate to high dose human albumin rich in DHA is neuroprotective in focal brain ischemia (25).

These observations lend credence to the notion that omega-3 fatty acids promote neuroprotection and neuroregeneration. These, along with its anti-inflammatory properties make it an attractive agent to study in the prevention and amelioration of paclitaxel induced peripheral neuropathy. We hypothesize that omega-3 fatty acid supplementation started prior to initiation and administration of chemotherapy can potentially attenuate paclitaxel induced nerve damage.

Omega 3 Fatty Acids and Paclitaxel

Currently, there are no documented safety concerns with the combination of omega-3 fatty acids and paclitaxel. On the contrary, preclinical and clinical studies have investigated the potential synergy with the combination treatment (26-28). In early preclinical data, sequential exposure to Omega-3 PUFA docosahexanoic acid (DHA) followed by paclitaxel or docetaxel was demonstrated to enhance cytotoxicity of taxanes against the metastatic breast cancer cell line MDA-MB-231 (26). The investigational drug Taxoprexin (DHA-Paclitaxel), a 2'-O-acyl conjugate of paclitaxel covalently bound to DHA via an ester bond, was developed to improve paclitaxel's therapeutic performance. Phase I trials did not show any dose limiting toxicities with the conjugated preparation (27). Oral omega-3 fatty acids, classified as a nutritional additive, have several commercial preparations available for over the counter use. To date, there are no reported adverse drug reactions with FDA approved Lovaza and paclitaxel.

Feasibility

P-APS is common and occurs in about 50-90% of patients. Paclitaxel is a common chemotherapeutic agent used in a variety of malignancies, both in the early and advanced setting. Therefore, it is expected that the many patients will be eligible for this clinical trial.

Omega-3 fatty acids have a well-established safety profile and have led to their wide availability and over the counter use. As detailed above, its anti-inflammatory properties and favorable side effect profile make them an attractive alternative to NSAIDS. Furthermore, its potential neuroprotective properties make them an intriguing candidate for testing in paclitaxel induced neuropathy.

This will be a multi-institutional study and the Principal Investigators are Zoneddy Dayao, MD (NCCTG) from the University of New Mexico Cancer Center and Debra Barton, RN, PhD (NCCTG) from the Mayo Clinic, Rochester, MN. Melanie Royce, MD, PhD (ACOSOG) from the University of New Mexico is a co-investigator. The primary site will be the New Mexico Cancer Care Alliance (NMCCA), as defined below.

New Mexico Cancer Care Alliance is a New Mexico nonprofit corporation established in February, 2002, that functions as a single point of contact for the management of oncology trials at multiple sites. NMCCA includes: University of New Mexico Cancer Research and Treatment Center; Lovelace Health Systems; the New Mexico Veterans Affairs Health Care System; Presbyterian Healthcare Services (Presbyterian Hospital, Presbyterian Kaseman Hospital, Presbyterian Medical Group); Memorial Medical Center, Christus St. Vincent Regional Medical Center; Hematology-Oncology Associates; New Mexico

Cancer Care Associates and New Mexico Ear, Nose, Throat Specialists, P.C.; PMG Surgery. It is a joint venture representing approximately 100 physicians in central, northern and southern New Mexico who are engaged in the care of cancer patients.

The NMCCA utilizes a centralized IRB for all participating sites: either the University of New Mexico Human Research Review Committee (HRRC), or the Western IRB. Each trial has only one full review regardless of how many sites will participate.

NMCCA has a strong commitment to clinical trial accruals. From 2010-2011, a total of 517 patients were enrolled in therapeutic and cancer control trials, with 229 from UNM and 288 from the other sites. The last 5 years have shown a steady increase in clinical trial enrollment, with a total of 2214 patients accrued at all sites from 2006-2011.

B. Aims

Primary

1. To determine whether omega-3 fatty acids can prevent or ameliorate paclitaxel associated pain syndrome (P-APS) in cancer patients.

Secondary

1. To determine whether omega-3 fatty acids can prevent development of peripheral neuropathy.
2. To assess tolerability of omega-3 fatty acids in this setting.
3. To compare QOL with omega-3 fatty acids supplementation versus placebo.

C. Study Plan

Eligibility criteria:

1. Patients have a diagnosis of breast cancer or ovarian cancer.
2. Patients must be ≥ 18 years old
3. Patients may be either male or female
4. Patients are scheduled to receive weekly paclitaxel at 70-90 mg/m2 for a minimum of 2 months. 3 out of 4 weeks is allowed.
5. ECOG Performance Status (PS) of 0, 1 or 2
6. Patients must not have taken omega-3 fatty acid supplements within the past 1 month prior to registration and must agree to refrain from use of omega-3 fatty acid supplements from sources outside the study.
7. Patients must not be on NSAIDS or aspirin for at least 1 week prior to registration. NSAIDS or aspirin are allowed after enrollment.
8. Patients must not have received any other analgesics (opiates and tramadol) 1 week prior to registration. Analgesics (opiates and tramadol) are allowed after enrollment.
9. Patients must have the ability to complete questionnaires by themselves or with assistance.

10. Patients must not be on anticoagulation medication (heparin/warfarin) within 28 days prior to registration, because of increased risk of bleeding.
11. Concurrent treatment with carboplatin +/- bevacizumab is allowed.
12. Concurrent treatment with Her2 neu targeted therapy is allowed.

Exclusion Criteria

1. Known allergy to omega-3 fatty acids, fish, or shellfish
2. Pre-existing diagnosis of peripheral neuropathy
3. Diagnosis of fibromyalgia
4. Concurrent planned neutrophil colony stimulating factor therapy
5. Prior exposure to paclitaxel within the last 6 months

Protocol Treatment:

Treatment: Omega-3 Fatty Acid: 4 capsules (1 gram/capsule) or a double-blinded placebo either once daily or 2 capsules two times daily beginning 1 week prior to starting paclitaxel and continued until 12 weeks or until paclitaxel is discontinued, whichever comes first (maximum of 12 weeks).

Rationale for dosing: A dose of at least 2.7 g/day of EPA and DHA have been reported to have analgesic effects in inflammatory conditions (11). The dose of 4 g/day is an FDA approved dose of omega-3 fatty acids (Lovaza) for the treatment of hypertriglyceridemia and has a well-documented toxicity profile. On the basis of this, a dose of 4 g/day was selected.

Formulation of omega-3-fatty acid: Lovaza (omega-3-acid ethyl esters) capsules will be used**.** Each 1-gram capsule of Lovaza contains approximately 465 mg EPA and 375 mg DHA.

Formulation of placebo: Placebo will be provided by Clinical Encapsulation Services or UNM Pharmacy. Excipient material will be microcrystalline cellulose. It will be odorless like Lovaza. Since the placebo may slightly differ from Lovaza, the pills will be dispensed in opaque bottles and providers will not be allowed to open them. In addition, to document blinding, the patients will be asked on cycle 1 Day 2, if they know what medication they are receiving.

Randomization: Clinical Encapsulation Services or UNM Pharmacy will package both placebo and active drugs. Our pharmacy will take care of randomization. Then our research nurses will dispense the drug.

Measurement tools:

For P-APS symptoms, there will be 4 types of questionnaires, adapted from NCCTG N08C1: (1) a baseline/pretreatment questionnaire. (2) a daily paclitaxel induced acute pain syndrome symptom log from Day 2-7 (2, 20). (3) day 8 P-APS symptom summary. (4) 1 month after completion of paclitaxel questionnaire.

For chemotherapy-induced peripheral neuropathy (CIPN) neurotoxicity, the EORTC-QLQ CIPN20 patient questionnaire will be used. The questionnaire will be filled out on the 8th day of each chemotherapy treatment and 1 month after completion of therapy.

Dietary counseling: As omega-3 fatty acid metabolism is affected negatively by the amount of arachidonic acid in the diet, dietary counseling will be provided to assess the fatty acid intake. Omega-3 and Omega-6 Fatty Acid Dietary Intake Questionnaire will be given at baseline, Week 2, Week 4 and monthly thereafter (prepared by Laura Taber, PhD).

Laboratory tests: Due to a small risk of increased LDL and transaminase levels, LDL and transaminase levels will be determined at baseline, at Week 4 and the last day of paclitaxel treatment.

D. Adverse Events

Adverse events (AEs) will be assessed according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0. Adverse events will be assessed to determine tolerability as part of the secondary objectives of the study. Analyses will be performed for all patients having received at least one dose of omega-3 (Lovaza). Recording of AEs and their attribution (whether they are due to omega-3 or due to standard of care chemotherapy treatment (paclitaxel) is important to determining the tolerability of omega-3. Since this study focuses on determining whether omega-3 can prevent P-APS and/or peripheral neuropathy as well as the tolerability of omega-3 in patients undergoing treatment with paclitaxel, the scope of AE collection will be limited to:

1) Any AEs involving aches or pain
2) Any AEs involving neuropathy
3) Any AEs that are definitely, probably, or possibly related to omega-3/placebo or paclitaxel

In addition to recording AEs, data will be captured on whether AEs attributed to omega-3 or AEs involving aches, pains, or neuropathy cause a given patient to discontinue participation in the study. Reported adverse reactions for omega-3 fatty acids are minimal. While none of these symptoms require dose modification or discontinuation for safety concerns, patients may discontinue therapy should they choose, or if they are experiencing significant discomfort. The common side effects reported in at least 3% or greater rate than placebo in prior clinical trials using Lovaza are as follows:

(1) Eructation (belching) which occurs in about 4%

(2) Dyspepsia occurring in about 3%

(3) Altered taste in about 4%

(4) As Lovaza contains omega-3 fatty acids obtained from several fish sources, patients with known hypersensitivity or allergy to fish/shellfish are excluded. However, a person who develops a rash on the 1st week of Lovaza treatment, prior to paclitaxel administration, should be evaluated for Lovaza allergy. The rash should be graded per NCI-CTAE version 4 criteria and be recorded as a possible Lovaza allergy.

Paclitaxel Side Effects: These should be reported per NCI-CTAE version 4. Dose modification of paclitaxel will be at the discretion of the treating physician.

Side effects of paclitaxel include:

1) neutropenia,
2) transaminitis,
3) neuropathy,
4) hypersensitivity reactions,
5) alopecia,
6) arthralgias
7) myalgias.

Patients who discontinue paclitaxel treatment due to allergy to paclitaxel will not be evaluable.

E. Data Analysis

In this pilot study, the effect of omega-3 on severity of paclitaxel associated pain syndrome will be evaluated in 60 patients using 1:1 randomization into omega-3 plus paclitaxel group and placebo plus paclitaxel group to achieve the primary aim. The primary endpoint will be determined by questions in N08C1 pain inventory. Mean severity will be calculated for each group and differences between groups will analyzed via t-tests or Wilcoxon rank-sum tests as appropriate. We will also consider a binary variable for incidence (no pain versus any pain, no relief versus any relief, does not interfere versus other) to evaluate the primary aim. A formal sample size justification based on statistical hypothesis is not applicable to this pilot study. Considering 60%-80% incidence of paclitaxel associated pain syndrome, we can detect a minimal difference of 37.6%-37.9% pain syndrome difference base on 5% significance level and 80% power with our proposed sample size. In this effect size calculation, the significance level actually achieved by this design is 2.2%-2.6%. Our sample size justification is based on primary aim with a binary variable of incidence.

Similarly, we will consider both continuous variables and binary incidence variable for the secondary aims. For continuous variables, t-tests or Wilcoxon rank-sum tests will be used. Fisher's exact test will be used for the incidence variable with 95% confidence intervals.

Patients will be evaluable regardless of the number of cycles of paclitaxel completed. A patient will be considered evaluable if they have completed a baseline pre-paclitaxel questionnaire and at least one questionnaire during paclitaxel treatment.

The study will last for approximately 5 years including data analysis.

F. Data Safety Monitoring:

Data Safety Monitoring will be done by the University of New Mexico Data Safety Monitoring Board.

G. Budget: See attached

H. References

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TEST SCHEDULE

Test and Procedures	Baseline (Baseline or <28 days after registration)	Daily, Days 2-7 following each paclitaxel dose	Day 8 following each paclitaxel dose	1 Month after completion of Therapy
Baseline Pre-Paclitaxel Questionnaire (Appendix 1)	**X**			
Toxicity (AE) Assessment	**X**		**X** **(+/- 3 days)**	**X**
Daily Paclitaxel-Induced acute pain Syndrome Symptom Log (Appendix II)		**X** **On Day 2 of cycle 1 only, patients will answer question #11		
Day 8 PAPS Symptom Summary Questionnaire (Appendix III)			**X**	
EORTC QLQ-CIPN20 Questionnaire (Appendix IV)			**X**	**X**
1 Month post paclitaxel Questionnaire (Appendix V)				**X**
Dietary Counseling	**X**			
Dietary Questionnaire (Appendix VI)			Week 2 and Week 4, then monthly thereafter	**X**
Lipid panel	**X**		Week 4	**X**
LFTs	**X**		Week 3 or 4	

APPENDIX I

Baseline Pre-paclitaxel Questionnaire

Patient Study ID Number: _____

Date:_____

Directions: Please answer the following questions:

1. Do you have any chronic aches and pains? (Circle Yes or No)

   Yes No

2. Do you regularly take pain medications? (Circle Yes or No)

   Yes No (If no, go to question 4)

3. If yes, please list the name of each medication:

   _____

   _____

4 How much of a problem was numbness and/or tingling in your hands or fingers **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No numbness or tingling										Numbness/tingling as bad as it can be

5 How much of a problem was numbness and/or tingling in your feet or toes **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No numbness or tingling										Numbness or tingling as bad as it can be

6. How much of a problem was burning or shooting PAIN in your hands and fingers **over the last week** (**circle one number)**?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as it can be

7. How much of a problem was burning or shooting PAIN in your feet or toes **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as it can be

Appendix II

Daily Paclitaxel- Induced Acute Pain Syndrome Symptom Log

Patient Study ID Number: _____

Day# _____ Date:_____

1. Please rate any aches/pains that are **NEW** since your last dose of paclitaxel, and that you think might be related to your chemotherapy treatment by circling ONE number that best describes your aches/pains at its **WORST in the last 24 hours**.

   0 1 2 3 4 5 6 7 8 9 10

   No Aches/pains as bad

   pain as can be

2. Please rate the same aches/pains by circling the ONE number that best describes your pain at its **LEAST in the last 24 hours**.

   0 1 2 3 4 5 6 7 8 9 10

   No Aches/pains as bad

   pain as can be

3. Please rate the same aches/pain by circling the ONE number that best describes your aches/pains on the **AVERAGE in the last 24 hours**.

   0 1 2 3 4 5 6 7 8 9 10

   No Aches/pains as bad

   pain as can be

4. Have you used nonprescription medication, like aspirin , Tylenol, Motrin, Ibuprofen or Advil, for the pain in the last 24 hours (Circle Yes or No)

   Yes No (If no, go to question 7)

5. If yes, please list the name of each medications

   _____ _____

   _____ _____

6. If yes, please rate by circling ONE number how helpful these nonprescription medications were in controlling your pain **in the last 24 hours**.

0 1 2 3 4 5 6 7 8 9 10

No Aches/pains as bad pain as can be

7. Have you used opioid medications like codeine, oxycodone or morphine for this pain in the last 24 hours (Circle Yes or No)

Yes No (If no, go to question 10)

8. If yes, please list the name of each medication:

_____ _____

_____ _____

9. If yes, please rate by circling ONE number how helpful these opioid pain medications were in controlling your pain in the last 24 HOURS.

0 1 2 3 4 5 6 7 8 9 10

Not helpful, Completely helpful

No pain control No pain after taking drug

10. Other comments:

_____

_____

11. Day 2 Cycle 1 only:

What drug do you think you are taking? Placebo Lovaza I don't know/ I can't tell

APPENDIX III

Day #8 Paclitaxel-induced Acute Pain Syndrome Symptom Summary

Patient Study ID Number: _____

Date:_____

Directions: Please answer the following questions:

1. Over the previous week, have you developed any **NEW** aches/pains that you did not have prior to your last dose of chemotherapy and that you think is from this chemotherapy?

   Yes No

   If **NO**, then you can skip to question 18.

2. Please rate any aches/pains that you have by circling **ONE** number that best describes your aches/pains at its worst **over the last week**.

0	1	2	3	4	5	6	7	8	9	10
No aches or pains										Aches or pains as bad as can be

3. Please place a **CHECK** mark (√) by all of the appropriate words that could be used to describe this pain?

   _____Sharp

   _____Dull

   _____Throbbing

   _____Cramping

   _____Stabbing

   _____Gnawing

   _____Burning-hot

   _____Aching

   _____Heavy

   _____Splitting

   _____Shooting

   _____Stinging

   _____Pulsating

4. Please place a **CHECK** mark (√) by the two words that are most descriptive of your pain:

_____Sharp

_____Dull

_____Throbbing

_____Cramping

_____Stabbing

_____Gnawing

_____Burning-hot

_____Aching

_____Heavy

_____Splitting

_____Shooting

_____Stinging

_____Pulsating

5. Please list any other words that might describe these aches/pains

_____
_____
_____

6. Please indicate where these **NEW** pains are/were located by placing a **CHECK** mark (√) next to the location(s), please mark all that apply:

_____Arms, above the elbow

_____Arms, between the elbows and wrists

_____Hands

_____Legs above knee

_____Legs, between the knee and ankles

_____Feet

_____Upper back

_____Lower back

_____Neck

_____Head

_____Chest

_____Abdomen

_____Hips

_____Shoulders

_____Other, please specify _____

7. Please note whether walking or standing increased any new pain that you had after the paclitaxel you received (Circle one number)

0	1	2	3	4	5	6	7	8	9	10
Not at all										Yes, quite a bit

8. Please note whether light touching of areas of pain increased any new pain that you had after the paclitaxel you received. (Circle one number)

0	1	2	3	4	5	6	7	8	9	10
Not at all										Yes, quite a bit

9. Have you used nonprescription medications, like aspirin, Tylenol, Motrin, ibuprofen or Advil, for this pain **over the last week?** (Circle yes or no)

Yes No (If no, go to question 12)

10. If yes, please list each medication and estimate how many you took of each over the past week:

Medication:	Number used over the past week:
_____	_____
_____	_____

11. If yes, please rate by circling **ONE** number how helpful these nonprescription medications were in controlling your pain **overall during the last week**.

0	1	2	3	4	5	6	7	8	9	10
Not helpful, no pain control										Extremely helpful, no pain after taking the drug(s)

12 Have you used opioid pain medications (e.g. codeine, oxycodone, morphine, etc) for this pain **over the last week**? (Circle Yes or No)

Yes No (If no, go to question 15)

13. If yes, please list each medication and estimate how many you took of each over the past week:

Medication:	Number used over the past week:
_____	_____
_____	_____

14. If yes, please rate by circling **ONE** number how helpful these opioid pain medications were in controlling your pain **overall during the last week.**

0	1	2	3	4	5	6	7	8	9	10
Not helpful, no pain control										Extremely helpful, no pain after taking the drug(s)

15 Have you used anything else (e.g. massage, whirlpool, stretching, etc) for this pain **over the last week**? (Circle Yes or No)

Yes No

16. If yes, please specify: _____

17. If yes, please rate by circling **ONE** number how helpful these things were in controlling your pain **overall during the last week.**

0	1	2	3	4	5	6	7	8	9	10
Not helpful, no pain control										Extremely helpful, no pain after taking the treatment (s)

18. How much of a problem was numbness and/or tingling in your hands or fingers **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No numbness or tingling										Numbness or tingling as bad as it can be

19. How much of a problem was numbness and/or tingling in your feet or toes **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No numbness or tingling										Numbness or tingling as bad as it can be

20. How much of a problem was burning or shooting PAIN in your hands or fingers **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as it can be

21. How much of a problem was burning or shooting PAIN in your feet or toes **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as it can be

22. Other comments:

_____

_____

APPENDIX IV

EORTC QLQ- CIPN20

Patient Study ID Number: _____

Date:_____

During the past week:	Not at all	A little	Quite a Bit	Very much
1. Did you have tingling fingers or hands?	1	2	3	4
2. Did you have tingling toes and feet?	1	2	3	4
3. Did you have numbness in your fingers/ hands?	1	2	3	4
4. Did you numbness in your toes or feet?	1	2	3	4
5. Did you have shooting or burning pain in your fingers/ hands?	1	2	3	4
6. Did you shooting or burning pain in your toes and feet?	1	2	3	4
7. Did you have cramps in your hands?	1	2	3	4
8. Did you have cramps in your feet?	1	2	3	4
9. Did you have problems standing or walking because of a difficulty feeling the ground under your feet?	1	2	3	4
10. Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
11. Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
12. Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
13. Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
14. Did you difficulty walking because your feet dropped downwards?	1	2	3	4
15. Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
16. Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
17. Did you have blurred vision?	1	2	3	4
18. Did you have difficulty hearing?	1	2	3	4
19. If you drive a car, did you have difficulty using pedals?	1	2	3	4
20. (Answer only if you are a man) Did you have difficulty getting or maintaining an erection?	1	2	3	4

Appendix V

Monthly Questionnaire after paclitaxel chemotherapy completion

Patient Study ID Number: _____

Date: _____

1. How much of a problem was numbness and/or tingling in your hands or fingers **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No numbness or tingling										Numbness or tingling as bad as it can be

2. How much of a problem was numbness and/or tingling in your feet or toes **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No numbness or tingling										Numbness or tingling as bad as it can be

3. How much of a problem was burning or shooting PAIN in your hands or fingers **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as it can be

4. How much of a problem was burning or shooting PAIN in your feet or toes **over the last week** (**circle one number**)?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as it can be

6. Other Comments:

.

APPENDIX VI

OMEGA-3 and OMEGA-6 FATTY ACID DIETARY INTAKE QUESTIONNAIRE

Patient Study ID Number: _____

Date:_____

Instructions: You will be asked to complete this form at the time of registration, and every two weeks for the first month of the study. After that, you will be asked to complete this form at the completion of the study.

By selecting one (1) box per line, please indicate your average use, during the past 2 weeks, of each specific food. Please select a box by marking an "X" in it for one serving, or two or more "X 's" for more than one serving.

3 oz = the size of a deck of cards

Food	Never or less than once per week	1 per week	2 per week	3 per week	4 per week	5 per week	6 per week	7 per week (every day)	2 per day	3+ per day
Whole egg										
Canned tuna fish (3 oz)										
Dark meat fish (i.e. salmon, mackerel, sardines, swordfish) (3 oz)										
White fish (3 oz)										
Shrimp or lobster (3 oz)										
Scallops (3 oz)										
Chicken – white meat (3 oz)										
Chicken – dark meat (3 oz)										
Turkey – white meat (3 oz)										
Turkey – dark meat (3 oz)										

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Beef (hamburger, ribs or steak) **(3 oz)**										
Pork (pork chop, ribs, ham or roast) **(3 oz)**										
Pork or beef chile or stew (1/2 cup)										
Chicken or pork posole (1/2 cup)										
Chicken or beef taco or burrito **(1 medium)**										

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APPENDIX VII

Dietary Information

Part of this study is to collect information regarding your diet since there are certain foods rich in arachidonic Acid that can lower the effects of omega-3 fatty acids.

Arachidonic Acid (omega-6) rich foods	EPA and DHA (omega-3) rich foods
Egg yolks	Fish
Chicken	Shellfish
Turkey	
Beef	
Pork	

APPENDIX VIII

INST 1211 Questionnaire Summary Checklist:

Patient Name: _____

Patient Study ID #: _____

Date Range: _____ to _____

This form is a checklist for use by the research coordinator. Please use this form at visits during which questionnaires are collected. After obtaining the patient's signature, please file this form in the patient's chart.

Questionnaires:

Baseline Pre-paclitaxel Questionnaire	☐ **Yes**	☐**No**	☐**N/A**
Daily Paclitaxel Induced Pain Syndrome Symptom Log	☐ **Yes**	☐**No**	☐**N/A**
Days 2 through 7 of Cycle _____			
Day 8 Paclitaxel-Induced Acute Pain Syndrome Symptom Summary	☐ **Yes**	☐**No**	☐**N/A**
EORTC QLQ-CIPN20	☐ **Yes**	☐**No**	☐**N/A**
Monthly Questionnaire after Paclitaxel Chemotherapy Completion	☐ **Yes**	☐**No**	☐**N/A**
Omega-3 and Omega-6 Fatty Acid Dietary Intake	☐ **Yes**	☐**No**	☐**N/A**

I have completed the above documents as indicated above and have returned them to the clinic on the date below.

_____ _____

Patient Signature Date

_____ _____

Study Team Member Signature Date

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How this pilot study will lead to an ALLIANCE protocol

This pilot study will explore the role of omega 3 fatty acids in preventing or ameliorating the severity of paclitaxel associated acute pain syndrome (P-APS) and development of peripheral neuropathy in cancer patients. This will be a multi-institutional study conducted by the University of New Mexico under the auspices of the New Mexico Cancer Care Alliance (NMCCA), a nonprofit corporation with approximately 100 physicians in central, northern and southern New Mexico. The NMCCA functions as a single point of contact for clinical trials. Through this organization, cooperative trials including NCCTG, ACOSOG and CALGB, have been opened and several patients have been accrued.

This feasibility trial will provide an opportunity for three investigators from the legacy groups to collaborate: Zoneddy Dayao, MD (NCCTG) , Debra Barton, RN, PhD (NCCTG) and Melanie Royce, MD, PhD (ACOSOG). This also provides an opportunity for mentoring a junior faculty in the conduct of symptom intervention trial. If the results are positive, a definitive ALLIANCE Phase III trial will be conducted. The legacy group NCCTG, now ALLIANCE have conducted and published the largest body of evidence in P-APS and CIPN. Well established methodologies as well as correlative studies from the NCCTG experience will be used to further enhance the design of the Phase III trial. Given the straightforward intervention schema and the high incidence of P-APS, rapid accrual to this trial is anticipated.

Other support for this project: Currently none.